temperature, and also reads on the whirlpool bath of instant claim 17 because according to white, the bath should be recirculated through cleansing means which suggest a simulation of a whirlpool with agitation. The vehicle can be in the form of a gel or a spray (claim 17).

Note that the instant application defines The superoxygenated compositions of the present invention as comprise at least about 55 ppm oxygen but find useful concentrations from about 45 to about 220 ppm. The oxygen level in the compositions depends on several factors, including the type of composition, the temperature, and other components, active or not, that may be added for various reasons such as stability, ease of application or to enhance absorption [0020]. Accordingly, White's composition reads on the instant definition.

Also the limitation of time sufficient to increase the subepithelial partial oxygen pressure from about 30% to about 120% above baseline pO_2 is considered inherent since the disclosed method of the prior art would cause the same effect on healing of the wound or burn.

According to the Examiner, White discloses a method of treating a wound with a "molecular oxygen containing member of a family of materials known as synthetic blood or blood substitute". This family of synthetic blood materials has a carrier that is perfluorocarbons as the indicated in the title of White "Use of Perfluorocarbons as Wound Treatment" or as indicated in claim 1 of White "substantially fluorinated carbon material or a mono or dibrominated derivative thereof having an ability to transport oxygen". In a passage referred to, and partially quoted by the Examiner, col. 4 line 14+ "the ability to transport oxygen is **related to the solubility of oxygen** in the materials and suggest that the perfluorinated materials will

definition of being superoxygenated even though the O_2 levels are extremely high as these levels are for dissolved oxygen. White does not disclose a liquid containing molecular oxygen present at levels that exceed the solubility of O_2 in the fluorocarbon. Even when the solubility of O_2 in a liquid is extremely high but the liquid is not supersaturated in O_2, the release of O_2 does not necessarily occur, as it is the relative affinity of O_2 in the two media and the ability to transport the O_2 into the O_2 deficient media that is important for partitioning between the two media. As the superoxygenated composition of the present invention contains O_2 dramatically above the levels of dissolved O_2, it can readily release its O_2 to a deficient media, tissue, and the form of microbubbles provides the ability to readily transport the O_2 into that media. Therefore, White does not disclose a superoxygenated composition and can not anticipate a method that employs a superoxygenated composition comprising oxygen microbubbles.

The superoxygenated composition of the present invention is also physically different that the "molecular oxygen containing member of a family of materials known as synthetic blood or blood substitute" of White. As the O_2 is dissolved in White, O_2 is present in a continuous liquid medium. As the O_2 is in microbubbles in the instant invention, O_2 is present primarily in a discontinuous gas medium dispersed in a liquid. As White does not disclose microbubbles, but rather dissolved O_2 it cannot read on the claimed superoxygenated composition of oxygen microbubbles of the present application. Employment of a dissolved gas can not anticipate the employment of a gas dispersed in a liquid.

According to the Examiner, the carrier of White comprises water. Applicant respectfully disagrees with this assessment. No claims include water as a possible carrier and the claimed and disclosed carrier is the perfluorocarbon. White discloses water in the specification (col 4 ln 3) for an emulsion with the carrier perfluorocarbon. Water does not contain high levels of O_2,

the O_2 remains dissolved in the perfluorocarbon, which is the carrier. Again, even with water present in a liquid-liquid emulsion with the carrier, it does not modify the substantially fluorinated carbon material containing molecular oxygen in a manner that the liquid can be defined as being superoxygenated.

Applicants respectfully submit that the superoxygenated compositions of oxygen microbubbles is patentably distinguishable from the substantially fluorinated carbon material containing molecular oxygen of White. Therefore, White cannot anticipate the present invention, and request that claims 1, 2, 4-6, 10, 11, and 13 be allowed.

In the Office Action the Examiner concluded that claims 1, 2, 4-8, 10, 11, and 13-19 are rejected under 35 U.S.C. 102(b) as being unpatentable over White US 4,366,169 in view of Ladin US 5,792,090 further in view of Kolta US 6,139,876.

The Examiner states with respect to White:

White is applied as discussed hereinabove.

White does not specifically disclose use of the method to treat anaerobic bacteria, the oxygen bubble size.

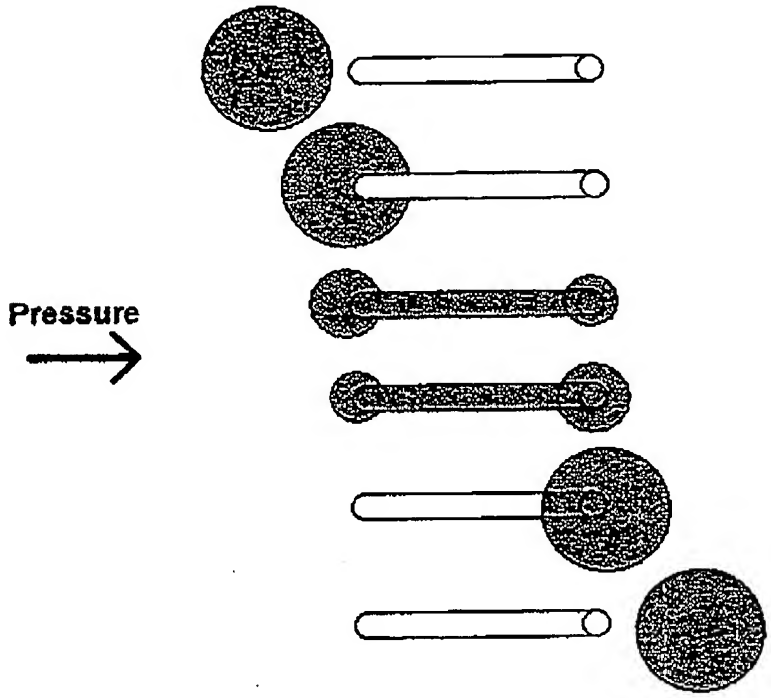
With respect to White the Examiner concedes that White does not disclose the oxygen bubble size of the present invention. Applicant respectfully submits, as indicated in detail above, that White does not disclose a composition with bubbles, which is why no bubble size is disclosed.

The Examiner states with respect to Ladin:

Ladin discloses a method of healing of surface wounds, including burns, which is facilitated by increasing the wound oxygen tension through the application of an oxygen-generating wound dressing which renewably and non-sustainingly chemically generates oxygen. The wound dressing contains an oxygen permeable membrane and an oxygen supply solution. Because the oxygen chemically produced by the subject invention may include both gaseous oxygen as well as dissolved oxygen, the membrane pore sizes of from 0.01 to 10 micron, preferably 0.1 to 1.0 microns are preferred to limit the oxygen passage (col. 5, lines 16+)

With respect to Ladin the Examiner states "Because the oxygen produced by the subject invention may include both gaseous oxygen as well as dissolved oxygen, the membrane pore sizes of from 0.01 to 10 micron, preferably 0.1 to 1.0 microns are preferred to limit the oxygen passage." Applicant respectfully disagrees with the interpretation of the section (col. 5, lines 16+) which discloses the use of the membranes. These membranes are to prevent transport of solid catalyst and dissolved salts, where it indicates removal of anionic and cationic species by absorption on the membrane, and to isolate pathogens greater than 0.45 microns, which is a restriction based on a non deformable particle size. Membranes of the type disclosed in Ladin will not stop any gas from being transported through the membrane from a high pressure side to a low pressure side, nor will it define a size of a bubble of a gas as it will not inherently provide a sheering force at the exit of the pore to break a large bubble into a small bubble. The gas transmissive abilities referred to in Ladin (col. 5 line 21) is necessarily relative to the rate at which gas can pass through the membrane and does not define an ability to define the size of a bubble. The pore size is the diameter of an open ended void through the membrane, and does not define the diameter of a deformable gas sphere that can pass through the pore. As with all membranes, any non-absorbed liquids and gases can deform to the shape of the pore and pass through the pore as illustrated below for a single large gas bubble encountering a single pore of a membrane. Therefore, the pore size cannot define the diameter of the bubble. As disclosed in Example 1 of Ladin, oxygen gas is generated and it is not in the form of a microbubble stable at ambient pressure as the pressure in a test apparatus rose to 5 atmospheres. Hence, Ladin can not

be combined with White to teach that a microbubble is formed, as no microbubble is formed and the gas can not be partitioned into microbubbles by the membrane of Ladin.



Transfer of a gas bubble through a pore of a membrane

Neither White nor Ladin teach or suggest that having oxygen in the form of a microbubble can be effective at increase the subepithelial partial pressure of oxygen. Furthermore, neither White nor Ladin demonstrates that the oxygen of their composition can pass through an epithelial layer. White claims treating a victim having a wound the normal healing of which is accelerated by exposure to oxygen, which comprises contacting the wound. White does not disclose passage of oxygen into the tissue to which the blood substitute is exposed. The wound dressing of Ladin is intended "to provide oxygen levels similar to those produced by moderate hyperbaric oxygen treatment" (col 3 ln 17-20) where hyperbaric oxygen treatment is stated to be a treatment where "the relative oxygen concentration of the deep dermis (1.8-2.2 mm) is unchanged" (col 1 ln 46-52). Hence, Ladin teaches away from expecting a surface treatment to increase subepithelial levels of O_2 when treating skin. Again the

combination of White with Ladin cannot suggest the novel ability of microbubbles to pass through epithelial tissue as has been observed for the microbubbles of the present invention.

The Examiner states with respect to Kolta:

Kolta discloses a gelatin with increased oxygen content for pharmaceutical, cosmetic and/or veterinary use. The gelatin comprises a gelling agent and a solvent, furthermore oxygen in a substantially even distribution with a pressure exceeding normal atmospheric pressure (abstract). Kolta teaches that gelatin and the oxygen encapsulated therein will have special synergetic effects. The intensive presence of oxygen will prevent proliferation of anaerobe bacteria which otherwise would rapidly multiply in the gelatin (col. 2 line 12+)

Accordingly, it would have been obvious to one skilled in the art at the time the invention was made to expand the teaching of White by realizing a fine size of the oxygen bubbles because the size of the bubble relate inversely with the penetration of the tissue and also to ensure the effect of the method on the anaerobic bacteria because Kolta discloses that the presence of oxygen ensures the prevention of proliferation of anaerobic bacteria. The expected result would be a method for increasing skin oxygenation by applying a composition of high oxygen concentration to a wound, or burn in a topical application or a bath.

With respect to Kolta, the Examiner states that Kolta discloses that a substantially even distribution with a pressure exceeding normal atmospheric pressure. According to the abstract of Kolta, "the surface tension of the gelatin is sufficiently high to retain at least a portion of the overpressure of the oxygen throughout a predetermined period of time after having been exposed ton atmospheric environment." This overpressure can not be significant. Consider the example of a soap balloon, which has a surface tension in the proximity of that one would expect with a liquid gelatin, the pressure differential on the inside of the bubble is not significantly greater than

that of the air for the bubble to expand. As indicted above considering White, the amount of oxygen is not as important a factor for oxygenation of tissue as having oxygen in excess of the equilibrium solubility in the carrier which is possible in the present invention due to the size of the microbubbles. The bubbles that form in the gelatins of Kolta are not microbubbles that have micrometer or nanometer dimensions. Microbubbles would not result in the scattering of light at the boundaries of the bubbles and would not cause an opaque appearance (col. 4 ln 40 – 46) as disclosed in Kolta. The size of the microbubbles for example compositions of the present invention were measured by a flow impedence device and could not be measured with a laser diffraction device (page 18 ln 1-6). The microbubbles of the present invention are described as being smaller than the bubbles released in a carbonated beverage, where a high proportion of the bubbles are not visible (page 6 ln 12-18). The bubbles formed upon the release of the pressure upon exposure to air in Kolta are necessarily large and are not microbubbles. As stated by the Examiner, Kolta teaches that the gelatin and the oxygen have a synergistic effect. As stated in Kolta, "**Oxygen transport** to deeper levels **is facilitated if the gelling agent**, from which the gel has been made, has components that can be absorbed by living tissues, and metabolism is further facilitated if the gelling agent can be utilized by eucariotic cells". Furthermore, Kolta teaches away from oxygen alone being able to heal tissue, stating, "We have supposed that during the absorption of proloxin the oxygen supply alone does not support the process of crating new tissues to a sufficient extent" (col. 14 ln 1-3). This synergistic effect can not be present in the superoxygenated composition of the present invention because it lacks the gelatin. Therefore, the composition of Kolta that teaches a synergistic effect without microbubbles can not obviate or motivate a superoxygenated composition which lacks the important synergistic component when Kolta teaches that oxygen alone is insufficient to promote heeling.

With respect to treatment of anaerobe bacteria, Kolta states that "The intensive presence of oxygen will prevent proliferation of anaerobe bacteria which otherwise would rapidly multiply in the gelatin" (col. 2 ln 12+) as pointed out by the examiner. Kolta begins the disclosure (col. 1 ln 10-24) by describing how gelatin normally promotes the proliferation of anerobe bacteria, stating, "It has been known for a long time that ossein-products like gelatin alba are excellent base materials for different kinds of pharmaceuticals. In room temperature the water based solution of such materials forms a gel if the concentration exceeds about 1-1.5%. It is also known that gels, especially gelatin can be used for treating different kinds of skin wounds, e.g.

burns or frost wounds. The gel is applied under a cover primarily for treating *combustio erythematosa*. It is also well-known in the art that gels, particularly gelatin are ideal media for bacterial cultures, and in the treatment of burn or frost wounds there is a dilemma whether gelatin can be used at all and whether such use should take place under a cover or not. The primary problem connected with a covered treatment lies in the potential danger of the proliferation of anaerobe bacteria." The storage of the gel in an oxygen rich form would keep anaerobe bacteria from getting into the gel prior to its introduction to the wound. Kolta does not disclose that the oxygen in the gel attacks anaerobe bacteria infections present in the wound, only that it will prevent their proliferation in the gel.

Therefore, one can not combine Kolta, which requires synergistic components not present in the present invention and does not teach that the treatment with the gel will kill anaerobe bacteria infections, with Ladin and White, which does not teach microbubbles or a superoxygenated composition, to render obvious the present invention which claims a method using a superoxygenated composition of oxygen microbubbles. Applicants respectfully request that claims 1, 2, 4-7, 10, 11, and 13-21 be allowed.

Applicants have made every effort to present claims that distinguish over the cited art, and it is believed that all claims are in condition for allowance. However, Applicants invite the Examiner to call the undersigned if it is believed that a telephonic interview (direct line (561). 671-3656) would expedite the prosecution of the application to an allowance. Although no fee is believed to be due, the Commissioner for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

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